

## INTERNATIONAL COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

Date of mailing (day/month/year) 21 June 2001 (21.06.01)	
International application No. PCT/US00/24949	Applicant's or agent's file reference HMR2021PCT
International filing date (day/month/year) 13 September 2000 (13.09.00)	Priority date (day/month/year) 14 September 1999 (14.09.99)
Applicant LEE, George, E. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 12 April 2001 (12.04.01)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number  
**WO 01/19832 A2**

(51) International Patent Classification<sup>7</sup>: C07D 498/04,  
A61K 31/40, 31/55, 31/501, 31/42, 31/44, 31/506, A61P  
25/18 // (C07D 498/04, 333:00, 261:00)

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(21) International Application Number: PCT/US00/24949

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09/396,156 14 September 1999 (14.09.1999) US

(63) Related by continuation (CON) or continuation-in-part  
(CIP) to earlier application:  
US 09/396,156 (CON)  
Filed on 14 September 1999 (14.09.1999)

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
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KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— Without international search report and to be republished  
upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: THIENISOXAZOLE PHENOXY UNSUBSTITUTED ETHYL AND PROPYL DERIVATIVES USEFUL AS D<sub>4</sub> AN-  
TAGONISTS

(57) Abstract: The compounds are of the class of thienisoxazole phenoxy unsubstituted ethyl and propyl derivatives, useful as D<sub>4</sub> antagonists. Said compounds are useful for the treatment of medical conditions mediated by inhibition of D<sub>4</sub> receptor. These conditions comprise, for example, Attention Deficit Hyperactivity Disorder, Obsessive-Compulsive Disorder, Psychoses, Substance Abuse, Substance Dependence, Parkinson's Disease, Parkinsonism, Tardive Dyskinesia, Gilles de la Tourette Syndrome, Conduct Disorder, and Oppositional Defiant Disorder. A further aspect of the invention is to provide a pharmaceutical composition, intermediates, and a method of making said class of compounds.

WO 01/19832 A2

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>HMR2021PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/US00/24949</b>	International filing date (day/month/year) <b>13/09/2000</b>	Priority date (day/month/year) <b>14/09/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D498/04</b>		
Applicant <b>AVENTIS PHARMACEUTICALS, INC. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  <b>12/04/2001</b>	Date of completion of this report  <b>27.12.2001</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Grassi, D</b>  Telephone No. <b>+49 89 2399 8499</b>



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/24949

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-90 as originally filed

**Claims, No.:**

1-109 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/24949

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 78,79,82-103.

because:

☒ the said international application, or the said claims Nos. (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-109
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-109
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-77,80,81,104-109

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/24949

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No: Claims

2. Citations and explanations  
**see separate sheet**

**R Item III**

Claims 78, 79 and 82-103 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

- 1) Reference is made to the following documents:  
D1: WO-A-98 18797
- 2) The subject-matter of present claims 1-109 is new (Article 33(2) PCT).
- 3) The subject-matter of claims 1-109 involves an inventive step (Article 33(3) PCT).

D1, being regarded as closest prior art, discloses methoxyphenylpiperazine derivatives exhibiting antipsychotic effects (cf. title)

The compounds of D1 bind to the D-2 dopamine receptor and contain a indoliziny- an imidazo[1,2-a]pyridinyl-, a imidazo[1,2-a]pyrimidinyl-, a dihydroimidazo[2,1-b]thiazolyl- or a imidazo[2,1-b]thiazolyl-group (cf. claim 1)

The technical problem underlying the present application is seen in the provision of alternative antipsychotic drugs.

The problem appears to be solved (cf. pages 80-90).

The present compounds according to claim 1 in which R1 and R2 form a piperaziny- ring are closely related to the compounds of D1, differing in the thieno[2,3-d]isoxazol- ring from the compounds of D1 which contain a 6- imidazo[2,1-b]thiazolyl-group.

The prior art does not prompt the skilled person to the present thieno[2,3-d]isoxazol ring and, due to a different point of attachment, the modification can not be regarded as isosteric replacement. Therefore, inventive activity can be acknowledged.

The claims 2-77 designate preferred embodiments and are therefore also inventive.

The claims 78, 79 and 82-107 relate to the use or the preparation of the inventive compounds. The claims 80 and 81 relate to compositions containing the compounds of claim 1. The claims 108 and 109 relate to intermediates in the preparation of the compounds of claim 1 and contain the thieno[2,3-d]isoxazol- ring. The said claims 78-109, therefore, also involve inventive activity.



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>HMR2021PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 24949</b>	International filing date (day/month/year) <b>13/09/2000</b>	(Earliest) Priority Date (day/month/year) <b>14/09/1999</b>
Applicant  <b>AVENTIS PHARMACEUTICALS, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

**4. With regard to the title,**

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/24949

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/04 A61K31/40 A61K31/55 A61K31/501 A61K31/42  
A61K31/44 A61K31/506 A61P25/18 //(C07D498/04, 333:00,  
261:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 18797 A (RICHTER GEDEON VEGYESZETI GYAR RT., HUNG.; LASZLOVSZKY, ISTVAN; DOMANY,) 7 May 1998 (1998-05-07) page 10 -page 15; examples claim 1  ---  -/--	1-109

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

13 March 2001

Date of mailing of the international search report

29/03/2001

Name and mailing address of the ISA

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Authorized officer

Paisdor, B

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/24949

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MAGDO, ILDIKO ET AL: "3D quantitative structure-activity relationship (CoMFA) study of heterocyclic arylpiperazine derivatives with 5-HT1A activity" retrieved from STN Database accession no. 134:141357 XP002162748 abstract; figures 22,23 &amp; MOL. MODEL. PREDICT. BIOACT., 'PROC. EUR. SYMP. QUANT. STRUCT.-ACT. RELAT.!, 12TH (2000), MEETING DATE 1998, 338-339. EDITOR(S): GUNDERTOFT KLAUS;JORGENSEN, FLEMMING STEEN. PUBLISHER: KLUWER ACADEMIC/PLENUM PUBLISHERS, NEW YORK, N. Y. ,</p> <p>-----</p>	1-109

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/24949

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818797 A	07-05-1998	HU 9603001 A	28-07-1998
		AU 4962097 A	22-05-1998
		BG 103370 A	31-05-2000
		BR 9712588 A	26-10-1999
		CN 1235606 A	17-11-1999
		CZ 9901320 A	11-08-1999
		EP 0935599 A	18-08-1999
		NO 992059 A	29-04-1999
		PL 333076 A	08-11-1999
		SK 49499 A	13-03-2000
		TR 9900946 T	21-07-1999
		TW 406083 B	21-09-2000
		US 6103724 A	15-08-2000